White Fox 4 mg Nicotine Pouch Products are Bioequivalent to 4 mg Nicorette Lozenge

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Abstract

White Fox brand (GN Tobacco Sweden AB) tobacco free nicotine pouches were tested to determine if the release and absorption of nicotine was equivalent to Nicorette® lozenges. The pharmacokinetics of nicotine absorption from White Fox All White Slim portion and Full Charge All White Regular portion pouches were assessed and compared to a 4 mg Nicorette mint flavor lozenge. A randomized, open label, crossover, in-patient clinical study was performed in 27 subjects to evaluate the nicotine plasma levels. Each study day, subjects used one of the test pouches or one Nicorette lozenge under controlled conditions for 60 minutes. Blood was collected for up to 12 hours. Geometric Least Square (LS) mean C_{max} values were similar for White Fox Slim and White Fox Regular when compared to Nicorette lozenge and the 90% confidence interval of the geometric mean ratio of the difference was within the predefined margin of 80% to 125%, indicating bioequivalence. Geometric LS mean AUC_{0-t} values were similar for White Fox Regular when compared with Nicorette lozenge. The 90% confidence interval of the geometric mean ratio of the difference for AUC_{0-t} was within the predefined margin of 0.80 to 1.25, indicating bioequivalence. Geometric LS mean AUC_{0-t} values were also similar for White Fox Slim when compared with Nicorette lozenge; however, for the AUC value, the lower bound of the 90% confidence interval of the geometric mean ratio of the difference was slightly below the predefined margin of 0.80, indicating slightly lower overall exposure for the White Fox Slim product compared with Nicorette lozenge, Since this is a consumer product that is used as desired, any small differences in the bioavailability are not likely to be clinically significant.

The Product

GN Tobacco's modern oral nicotine pouches were developed as an alternative delivery system to conventional nicotine replacement therapy products such as Health Canada approved nicotine gums or lozenges. GN's products are made by applying food-grade flavors, pharmaceutical-grade USP nicotine, salt, water, humectants, and pH modifiers to microcrystalline cellulose. The white powder is enclosed in a fleece pouch material similar to traditional tobacco snus products (**Figure 1**).

The product does not contain any tobacco leaf or tobacco stem material, but it does contain nicotine and is intended to emulate pharmacokinetic (PK) aspects of traditional nicotine replacement therapy products. The products are intended to be placed in the mouth between the cheek and gum for a period of time determined by the user (typically between 30 to 60 minutes).

The White Fox Regular product weighs 1000 mg measuring 18 x 32 mm and the Slim product weighs 750 mg measuring 14 x 32 mm. Both products are designed to contain 4 mg of nicotine.

Figure 1. White Fox Pouch Product

Methods

This was a randomized, open-label, crossover study designed to evaluate the nicotine PK of White Fox All White Slim (Slim) portion and Full Charge All White Regular (Regular) portion pouches containing 4 mg nicotine compared to 4 mg Nicorette mint flavor lozenge in healthy adult male and female smokers who have experience using smokeless tobacco products.

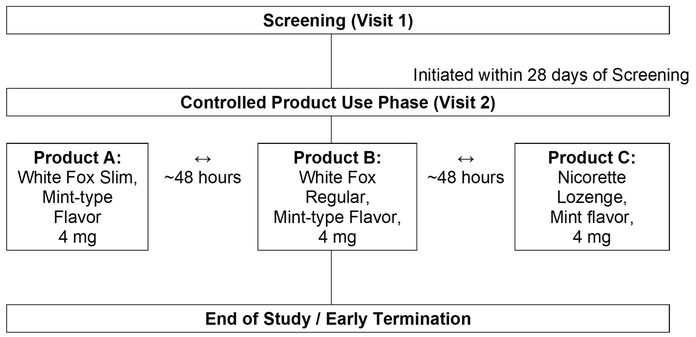
Subjects were required to have a history of smoking an average of ≥10 cigarettes daily for at least 1 year and were required to have used a smokeless tobacco product at least once in their lifetime. Subjects also had to test positive for urine cotinine (≥500 ng/mL) at Screening indicating they were smokers.

Subjects participated in a Standard Screening visit and a Confined Assessment Phase, which included a Product Trial Session on Day -1 and Product Use Session. Each study day of product use was separated by approximately 48 hours. Subjects consumed one lozenge or placed the pouch in their mouth between the cheek and gum for 60 minutes. Blood sampling was within 5 minutes of start of product use (Time 0; T0) and at 5, 10, 15, 20, 30, 45, 60, 90, 180, 360, and 720 minutes after product administration.

Study Design

Figure 2 shows the study design. The bioequivalence analysis was conducted using a linear mixed models in SAS 9.4® using the MIXED procedure. This statistical technique is used to account for the repeated measures resulting from the study's crossover design. For these models, the study subject was specified as the random effect, with the final model being characterized as a random effects mixed model. The outcomes for the analysis were log transformed peak nicotine concentration (C_{max}) and Area Under the Curve (AUC) for T0 to the last quantifiable concentration (AUC_{0-t}). Bioequivalence was concluded if the 90% confidence interval of the AUC ratio of geometric least squared means was entirely within the range of 80%-125%. This range for evaluation is standard in PK bioequivalence studies.

Figure 2. Study Design



Results

A total of 29 subjects were randomized and 27 subjects completed the study. All subjects reported smoking approximately 16 – 17 cigarettes a day and had been smoking for approximately 24 years.

Nicotine plasma levels were measured after controlled use of the products. The White Fox Pouch products contained 4 mg of nicotine and the Nicorette lozenge was labeled 4 mg nicotine.

Figure 3 shows the baseline adjusted plasma nicotine concentrations of each product and **Table 1** shows the derived nicotine parameters. The White Fox products and the Nicorette lozenge use nicotine polacrilex. The nicotine polacrilex complex is intended to control the release of nicotine. The lozenge product is designed to be fully consumed (dissolved in the mouth) whereas the pouch is removed after 60 minutes. The time to peak nicotine absorption from the White Fox pouches was same as the lozenge (T_{max} = 45 minutes for both). The maximum amount of nicotine absorbed (C_{max}) was similar for the products with a mean (±SD) of 11.4 ± 3.1 ng/ml for Slim and 11.7 ± 3.1 ng/ml for the Regular product compared to 12.7 ± 4.6 ng/ml for the Nicorette lozenge. The AUC after 12 hours for the products was also very similar (2307 ng*h/ml for Slim product, 2747 ng*h/ml for Regular product and 2554 ng*h/ml for the Nicorette lozenge).

The bioequivalence (BE) analysis (**Table 2**) showed that the White Fox products were bioequivalent to the Nicorette lozenge for C_{max}. The geometric mean ratio of the AUC_{0-t} for the Regular product was 1.03 (0.85 – 1.25) and fell entirely within the 80%-125% range indicating BE between the Regular and Nicorette product. The geometric mean ratio of the AUC_{0-t} for the Slim product was 0.91 (0.75 – 1.10) indicating Slim product delivered slightly less nicotine overall compared to the Nicorette Lozenge over the 12-hour sampling period.

Overall, peak nicotine exposure for White Fox products was similar to that of Nicorette lozenge when used as directed. Overall nicotine exposure is similar or slightly lower than (Slim product) that of Nicorette lozenge. Under ad libitum consumer use of an over-the-counter product, the effects can be expected to be essentially the same for White Fox products and Nicorette lozenge. Any small differences in the bioavailability are not likely to be clinically significant.

Results

Figure 3. Baseline Adjusted Plasma Nicotine Concentrations

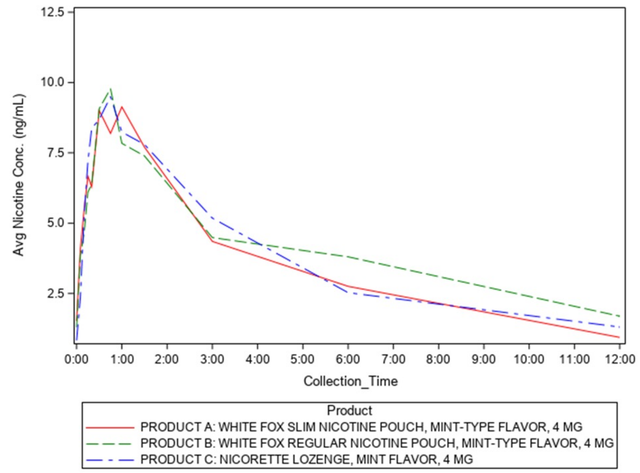


Table 1. Nicotine Pharmacokinetic Parameters

Parameter	White Fox All White Slim	White Fox Full Charge All White Regular	Nicorette Lozenge
C_{max} (ng/mL)			
N	27	27	27
Mean (SD)	11.43 (3.05)	11.69 (3.73)	12.66 (4.56)
AUC_{0-t} (ng-h/mL)			
N	26	27	26
Mean (SD)	2307.24 (902.89)	2746.50 (1325.55)	2553.71 (1178.75)
T_{max} (Minutes)			
N	27	27	27
Median	45	45	45

Table 2. Bioequivalence Parameters

Parameter	Geometric Mean Ratio (90% CI)	
	White Fox All White Slim Portion vs. Nicorette Lozenge	White Fox Full Charge All White Regular vs. Nicorette Lozenge
C_{max} (ng/mL)	0.93 (0.82,1.04)	0.93 (0.82,1.05)
AUC_{0-t} (ng·h/mL)	0.91 (0.75,1.10)	1.03 (0.85,1.25)

Conclusions

The White Fox Brand Pouch product is designed to emulate the pharmacokinetic aspects of nicotine replacement therapy products. This study was designed to demonstrate bioequivalence to an approved cessation product in Canada. GN Tobacco makes no smoking cessation claims about the product in the United States. **The analysis presented here indicates that the White Fox products are bioequivalent to a Nicorette 4 mg nicotine lozenge.**

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